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ORIGINAL REPORT

Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

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A B S T R A C T

Purpose
Salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT) is the standard treatment for relapsed diffuse large B-cell lymphoma (DLBCL). Salvage regimens have never been compared; their efficacy in the rituximab era is unknown.

Patients and Methods
Patients with $CD20^+$ DLBCL in first relapse or who were refractory after first-line therapy were randomly assigned to either rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). Responding patients received high-dose chemotherapy and ASCT.

Results
The median age of the 396 patients enrolled (R-ICE, n = 202; R-DHAP, n = 194) was 55 years. Similar response rates were observed after three cycles of R-ICE (63.5%; 95% CI, 56% to 70%) and R-DHAP (62.8%; 95 CI, 55% to 69%). Factors affecting response rates ($P < .001$) were refractory disease/relapse less than versus more than 12 months after diagnosis (46% *v* 88%, respectively), International Prognostic Index (IPI) of more than 1 versus 0 to 1 (52% *v* 71%, respectively), and prior rituximab treatment versus no prior rituximab (51% *v* 83%, respectively). There was no significant difference between R-ICE and R-DHAP for 3-year event-free survival (EFS) or overall survival. Three-year EFS was affected by prior rituximab treatment versus no rituximab (21% *v* 47%, respectively), relapse less than versus more than 12 months after diagnosis (20% *v* 45%, respectively), and IPI of 2 to 3 versus 0 to 1 (18% *v* 40%, respectively). In the Cox model, these parameters were significant ($P < .001$).

Conclusion
In patients who experience relapse more than 12 months after diagnosis, prior rituximab treatment does not affect EFS. Patients with early relapses after rituximab-containing first-line therapy have a poor prognosis, with no difference between the effects of R-ICE and R-DHAP.

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INTRODUCTION

During the last decade, the addition of the anti-CD20 monoclonal antibody rituximab to various chemotherapies[1-3] has dramatically improved response rates in diffuse large B-cell lymphoma (DLBCL), with complete responses (CRs) in 75% to 80% of patients. The use of rituximab in first-line treatment improved 5-year event-free survival (EFS) from 29% to 47% in the initial study of patients between age 60 and 80 years[4] and improved 3-year EFS from 59% to 79% in patients age 18 to 60 years;[5] rituximab was also associated with improved overall survival (OS). Before the rituximab era, 5-year OS rate for relapsed DLBCL was 53% after high-dose chemotherapy with autologous stem-cell transplantation (ASCT).[6] Various parameters greatly affect the results of ASCT, including chemotherapy sensitivity before ASCT,[7] time from diagnosis to relapse of less than 12 months,[8] and the presence of prognostic factors at relapse, as defined by the secondary age-adjusted International Prognostic Index (saaIPI).[9,10] The addition of rituximab to second-line chemotherapy followed by ASCT significantly improved progression-free survival (PFS) in patients not exposed to rituximab as part of their first-line treatment.[11]

For patients who have experienced relapse, no comparative studies have thus far been performed to our knowledge to evaluate the efficacy of the different salvage regimens.[12] Therefore, we compared the effects of two established salvage regimens

followed by ASCT, attempted to identify the parameters influencing the effectiveness of each regimen, and aimed to establish whether or not the widespread use of rituximab as part of first-line therapy affects the outcome of patients with relapsed DLBCL.[6]

The present Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) study was a collaborative effort by 12 countries worldwide. Patients with refractory or relapsed $CD20^+$ DLBCL were randomly assigned to one of the following two widely used regimens that included rituximab: rituximab, ifosfamide, carboplatin, and etoposide (R-ICE)[13] or rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP).[14] In responding patients, peripheral progenitor cells were collected after chemotherapy and reinfused after a high-dose chemotherapy conditioning regimen. We also investigated the impact of post-transplantation rituximab administration. Here, we report the results of the comparison between these two salvage regimens and the factors affecting outcome.

PATIENTS AND METHODS

Patients

Eligible patients were age 18 to 65 years and had aggressive $CD20^+$ B-cell non-Hodgkin's lymphoma, including DLBCL, and had experienced relapse or did not achieve CR with a standard anthracycline-based regimen composed of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Before enrollment, $CD20^+$ aggressive B-cell lymphoma was histologically confirmed in all patients. Patients eligible for inclusion had a performance status of 0 to 1. Exclusion criteria included CNS involvement, a history of HIV infection, post-transplantation lymphoproliferative disorders, and inadequate organ function. Patients were fully evaluated by examinations that included thoracic and abdominal computed tomography scans and bone marrow biopsy. saaIPI factor status was determined by the absence or presence of risk factors, poor performance status, elevated lactate dehydrogenase, and disseminated stage before salvage treatment.[9,10] The study was approved by the

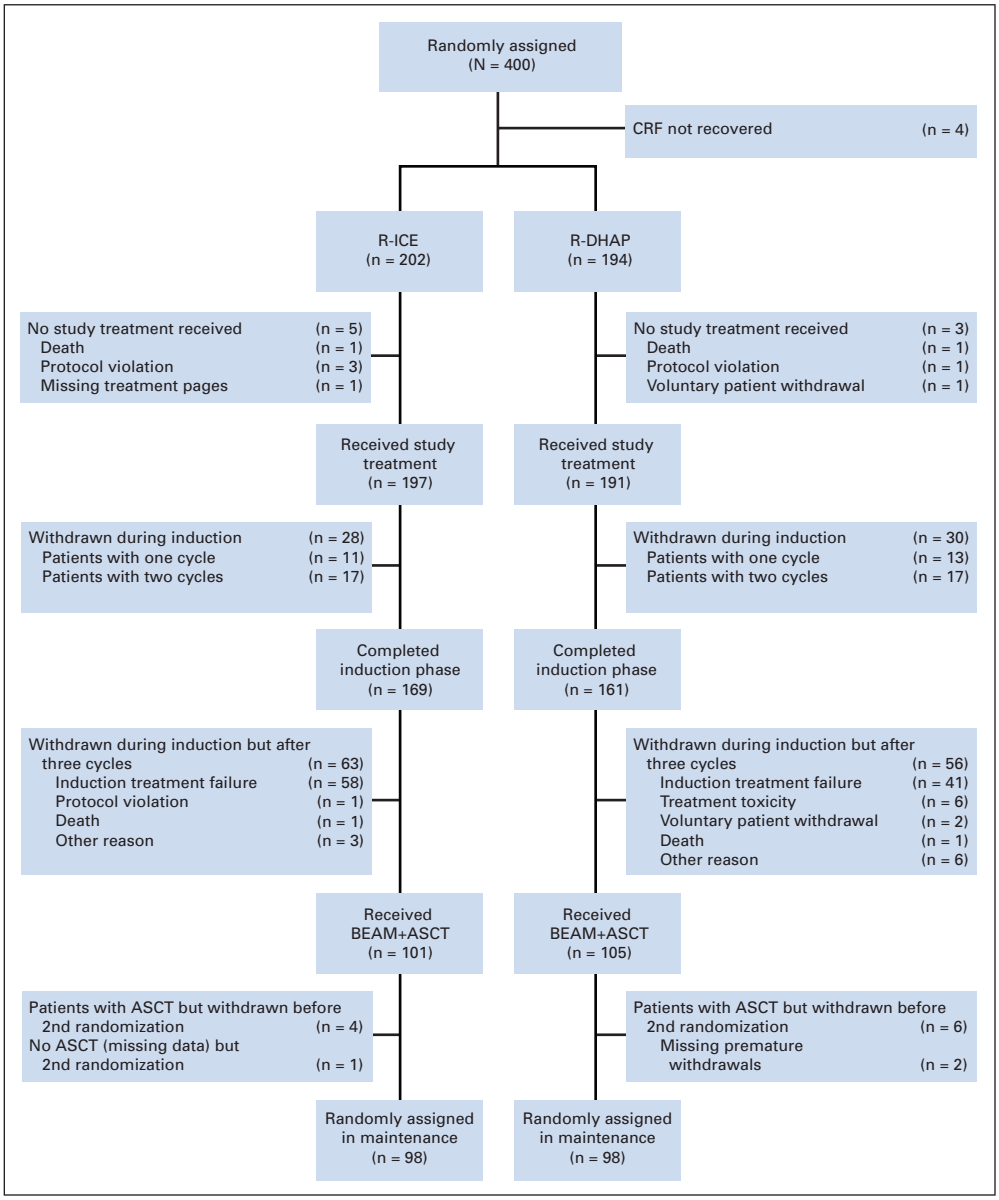

Fig 1. CONSORT diagram of distribution of patients according to arm resulting from the first random assignment. CRF, case report forms; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; BEAM, carmustine, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation.

relevant institutional review boards or ethics committees, and all patients gave written informed consent.

The study was registered under Europen Union Drug Regulating Authorities Clinical Trials (EudraCT) No. 2004-002103-32 and ClinicalTrials.gov NCT 00137995. Four hundred patients were enrolled between July 2003 and September 2007 for part 1 of the study. On an intent-to-treat basis, 396 patients were randomly assigned (202 patients to the R-ICE arm and 194 patients to the R-DHAP arm), and 388 patients were actually treated (Fig 1). Patient characteristics are listed in Table 1. No significant differences between the two arms were observed. Histology was reviewed by local hematopathologists attached to the participating centers. In addition, an international central review was performed in 289 (73%) of 396 patients. Only 13 patients did not have DLBCL; three patients had grade 3 follicular lymphoma, six patients had grade 2 follicular lymphoma, two patients had T-cell lymphoma, and two patients had Hodgkin's lymphoma. Only four patients were $CD20^-$, and CD20 status was not documented in 13 patients. All of the patients were included in an intent-to-treat analysis and received the protocol arm.

Study Design and Treatment

This study was a phase III multicenter randomized trial designed to compare the efficacy of R-ICE and R-DHAP in patients with previously treated DLBCL followed by ASCT with or without rituximab maintenance therapy (Fig 2). There were two random assignments, the first for salvage therapy and the second for maintenance treatment. The efficacy of the two salvage regimens is the subject of this report.

Patients were stratified according to participating country, prior rituximab treatment, and relapse occurring less than or more than 12 months after diagnosis. Every 3 weeks, patients were given three cycles of chemotherapy, followed by ASCT. In both regimens, rituximab (375 mg/m^2) was administered before chemotherapy, and in the first course, additional rituximab was given on day −1. The R-ICE[13] regimen consisted of etoposide (100 mg/m^2 per day) on days 1 through 3, ifosfamide (5,000 mg/m^2) infused continuously for 24 hours on day 2 with mesna; and carboplatin (area under the curve = 5; maximum dose, 800 mg) on day 2. The R-DHAP regimen[14] consisted of cisplatin (100 mg/m^2) on day 1 via continuous 24-hour infusion, followed on day 2 by cytarabine (2 g/m^2) in a 3-hour infusion repeated after 12 hours, and dexamethasone (40 mg/d) for 4 consecutive days. Granulocyte colony-stimulating factor was administered after R-ICE and, depending on site policy, with R-DHAP, but always after the third cycle until the end of leukaphereses.

Leukaphereses were performed after the third or second course of salvage therapy to obtain a target of 2,000,000 $CD34^+$ hematopoietic stem cells per kilogram for cryopreservation. In case of inadequate peripheral stem-cell collection after the third course, patients were considered to be experiencing treatment failure and withdrawn from the study.

Table 1. Baseline Patient Demographics and Clinical Characteristics (intent to treat)

Demographic or Clinical Characteristic	No. of Patients: R-ICE (n = 202)	No. of Patients: R-DHAP (n = 194)	P
Age, years			
Median	54	55	
Range	19-65	19-65	NS
Sex			
Male	125	118	
Female	77	76	NS
Ann Arbor stage			
I-II	81	66	
III-IV	119	121	NS
Extranodal site > 1	55	64	NS
Bone marrow involvement	17	19	NS
Elevated LDH	104	94	NS
saaIPI at relapse			
0-1	119	107	
2-3	75	74	NS
Time to relapse after diagnosis, months	89	87	NS
< 12*	112	103	
≥ 12	122	122	NS
Prior rituximab treatment			
Prior first-line CHOP-like chemotherapy	171	167	NS
Intensified CHOP	28	23	

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; NS, not significant; LDH, lactate dehydrogenase; saaIPI, secondary age-adjusted international prognostic index at relapse; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone.

*Including patients not achieving complete response after first-line treatment.

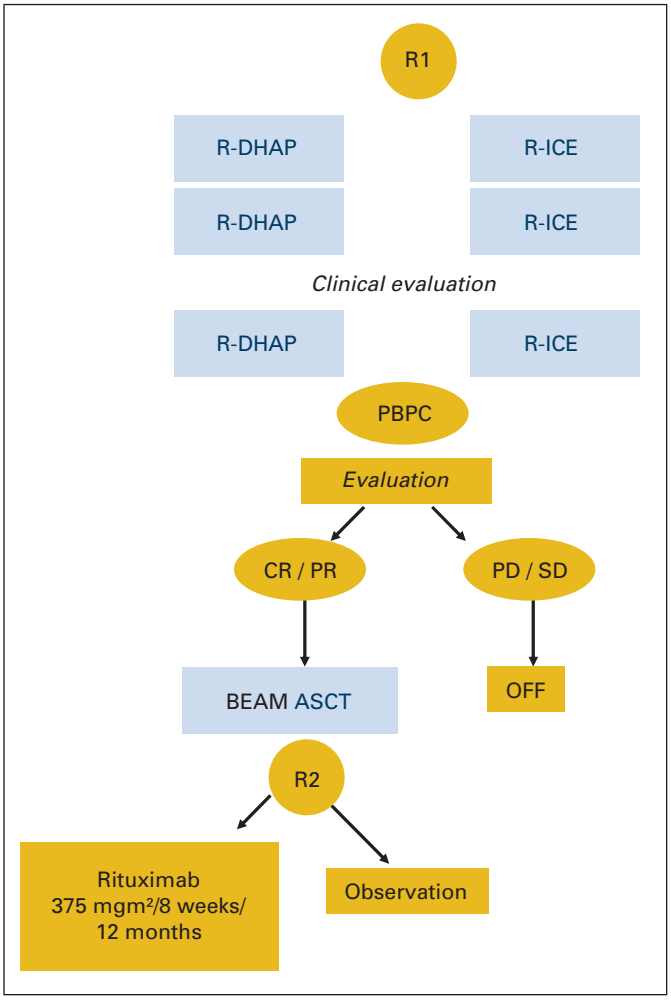

Fig 2. Treatment protocol. R1, first random assignment; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; PBPC, peripheral-blood progenitor cells; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; BEAM, carmustine, etoposide, cytarabine, melphalan; ASCT, autologous stem-cell transplantation; R2, second random assignment.

Assessment of Response and Follow-Up

Response was assessed by conventional diagnostic methods, including computed tomography scans, after the third chemotherapy course. Bone marrow biopsies were only repeated if abnormal before treatment.

Response was assessed using the International Working Group criteria.[15] CR was defined by the disappearance of all documented disease; unconfirmed CR (CRu) was used when a residual mass was present without evidence of

Table 2. Response After Induction Treatment (including death) for All Patients

Response	R-ICE (n = 197) No. of Patients	%	R-DHAP (n = 191) No. of Patients	%
Complete response	48	24	53	28
Unconfirmed complete response	24	12	22	12
Partial response	53	27	45	24
Stable disease	23	12	22	12
Progressive disease	38	19	35	18
Death	6	3	10	5
Premature withdrawal, not evaluated	4	2	4	2
Autologous transplantation				
Median $CD34^+$ cells collected, million/kg	4.5		4.9	
Collection failure < 2,000,000 $CD34^+$ cells	20	10	15	8
Mobilization-adjusted response	103	52.3	104	54.5
Consolidation with BEAM performed per protocol	101	51	105	55

Abbreviations: R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; BEAM, carmustine, etoposide, cytarabine, and melphalan.

active disease. Partial response (PR) was defined as a 50% reduction of measurable disease. The mobilization response rate was defined as the objective CR and PR rates associated with the target mobilization of the peripheral stem cells (2,000,000 $CD34^+$ hematopoietic stem cells/kg). Response was evaluated 3 months after transplantation. Follow-up procedures included a physical examination every 3 months for the first year and every 6 months thereafter for 2 years and a complete evaluation at the end of the first year or earlier if necessary.

ASCT

Patients who achieved a CR or PR after the third cycle of salvage treatment were given carmustine, etoposide, cytarabine, and melphalan (BEAM) high-dose chemotherapy. The BEAM regimen included carmustine (300 mg/m^2) on day −6, etoposide (200 mg/m^2), cytarbine (200 mg/m^2) on days −5 to −2, and melphalan (140 mg/m^2) on day −1. Peripheral-blood stem cells were reinfused on day 0, at least 24 hours after completion of BEAM.

Radiotherapy after transplantation was not allowed and was considered to be an event. Supportive treatments were given according to standard use in each center.

Statistical Analysis

The primary end point was the mobilization-adjusted response rate after three cycles of chemotherapy. A higher favorable response rate was expected for R-ICE than for R-DHAP, with fewer failed stem-cell collections. To detect a difference of 15% in the mobilization-adjusted response rate between R-ICE, for which this rate was 60% (75% response minus 15% mobilization failure), and R-DHAP, with a corresponding rate of 45% (65% response minus 20% mobilization failure) with a power of 82% and a 5% significance level, 400 patients had to be randomly assigned to the two chemotherapy arms. This allowed the second random assignment of 240 patients, with an expected dropout rate of 40% (Appendix, online only).

Administration of an alternative treatment was considered as an event. EFS was defined as the time from the start of treatment to progression, relapse, new treatment, or death (irrespective of cause), whichever event occurred first. PFS was defined as the time from study entry until disease progression or death. OS was defined as the time from the start of treatment to death.

The Kaplan-Meier method was used to estimate EFS, PFS, and OS, and 95% CIs were calculated.[16] Cox regression analysis was used to calculate the hazard ratio between the two arms.[17] All reported *P* values are two-sided, and $P < .05$ was considered significant. All analyses were carried out with SAS 9.1.3 software (SAS Institute, Cary, NC).

The study was designed by the Steering Committee of CORAL. The same investigator (C.G.) checked the data for medical coherence, analyzed and interpreted the data, and was the principal writer of this article (Appendix).

RESULTS

Response to Treatment

At diagnosis, 62% of the patients had been treated with a CHOP-like regimen with rituximab. Before inclusion, after first-line treatment, 65% of patients had achieved a first CR, 20% had achieved a PR, 4% had stable disease, and 11% had progressive disease.

After salvage chemotherapy but before transplantation, the overall response rate, including CR, CRu, and PR, was 63.5% (95% CI, 56.8% to 70.7%) in the R-ICE arm and 62.8% (95% CI, 55.6% to 69.7%) in the R-DHAP arm (Table 2). The factors significantly affecting the overall response rate in the univariate analysis ($P < .001$) were refractory disease/relapse less than 12 months after diagnosis, secondary IPI of 2 to 3, and prior rituximab treatment, but not the treatment arm (Table 3). In total, 206 patients received BEAM and ASCT per protocol, and five more patients had stable disease. The main reason for premature withdrawal from the study was disease progression (Fig 1). Three months after transplantation and random assignment, 132

Table 3. Response Rate and Survival According to Prognostic Factors

Factor	Total No. of Patients	Response CR/CRu/PR No. of Patients	%	*P*	3-Year Event-Free Survival %	*P*	3-Year Overall Survival %	*P*
All patients	398	246	63		31		50	
CR/CRu		148	38		51		70	
Prior rituximab								
No	147	122	83	< .001	47	< .001	66	< .01
Yes	244	124	51		21		40	
Relapse, > 12 months	160	140	88	< .001	45	< .001	64	
Refractory, < 12 months	228	106	46		20		39	< .001
saaIPI								
< 2	224	160	71	< .001	40		62	
> 1	146	76	52		18	< .001	32	< .001

Abbreviations: CR, complete response; CRu, unconfirmed complete response; PR, partial response; saaIPI, secondary age-adjusted International Prognostic Index.

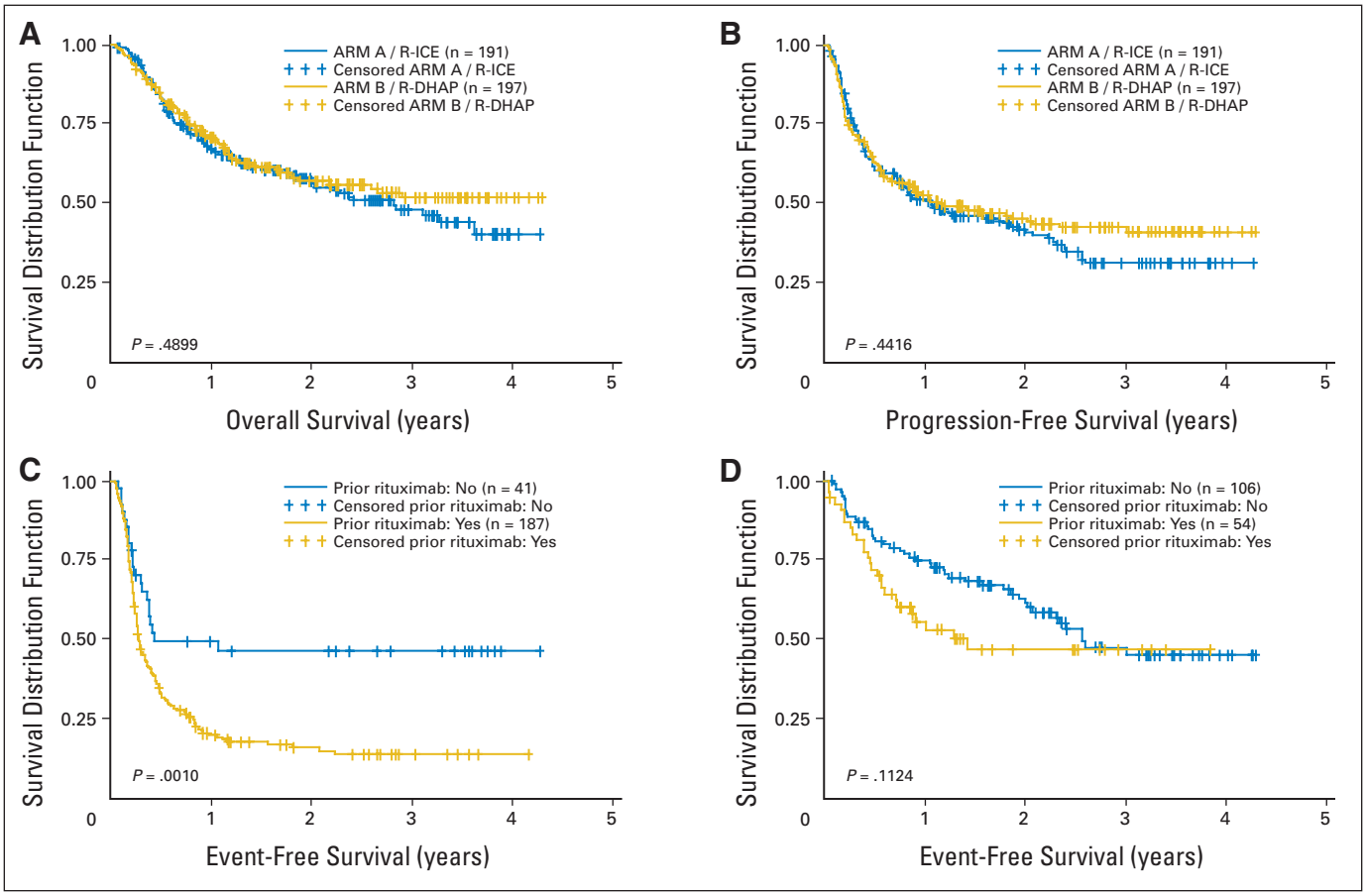

Fig 3. (A) Overall survival according to the first random assignment (intent to treat). (B) Progression-free survival according to treatment arm. (C) Event-free survival (EFS) according to prior rituximab treatment and relapse less than 12 months after diagnosis. (D) EFS according to prior rituximab treatment and relapse more than 12 months after diagnosis. R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, cisplatin.

(73%) of 181 evaluable patients had CR or CRu, 24 (13%) had PR, one had stable disease, and 17 (9%) had progressive disease.

Survival

After a median follow-up time of 27 months, the 3-year EFS rate was 31% (95% CI, 26% to 36%) and was not significantly different between the R-ICE and R-DHAP arms (26% and 35%, respectively; $P = .6$). Three-year PFS was 37% (95% CI, 31% to 42%), and again, the R-ICE and R-DHAP arms were not significantly different (31% and 42%, respectively; $P = .4$). Three-year OS (Figs 3A and 3B) was 49% (95% CI, 43% to 55%), with no difference between the R-ICE and R-DHAP arms (47% and 51%, respectively; $P = .4$). For patients who underwent ASCT, 3-year PFS was 53% (Fig 4A). There was no difference between the numbers of patients who achieved CR and PR just before ASCT (Fig 4B).

Three-year EFS, PFS, and OS were affected by prior rituximab treatment, early relapse, and saaIPI (Table 3). In the Cox model, all of these parameters remained significant ($P < .001$) for EFS, PFS, and OS; prior rituximab treatment was significant at a lower level ($P = .01$). The treatment arm was not significant.

When patients were analyzed according to early relapse and prior rituximab treatment, there was no difference in PFS, EFS, or OS for patients with relapse more than 12 months after diagnosis (Figs 3C and 3D). Early relapse and prior rituximab treatment (n = 187) defined a population with a poor response rate to the standard treatment; thus, their 3-year PFS was only 23%. However, for responding patients who underwent ASCT (n = 68), 3-year PFS was 39%, compared with 14% for patients who did not receive transplantation (n = 119; $P < .001$; Appendix Fig A1, online only). At the time of our analysis, 92 deaths (47%) had occurred in the R-ICE arm, and 82 deaths (43%) had occurred in the R-DHAP arm, mainly as a result of lymphoma.

Relapse and Progression

Progression or relapse was experienced by 104 patients in the R-ICE arm and 97 patients in the R-DHAP arm, mostly at the initial site and by half of patients during the treatment period. Various treatments were administered, including radiotherapy and chemotherapy, with or without transplantation (32 autotransplantations and 14 allografts; Appendix Tables A1 to A3, online only). A second CR was experienced by 32 of 176 patients. In all, 48 patients, 24 in each treatment arm, reported an event as a result of a new treatment after progression.

Adverse Events

The median time between salvage cycles was 22 days for both arms for the 230 patients who completed three cycles. Grade 3 to 4 hematologic toxicities were more severe in the R-DHAP arm than the

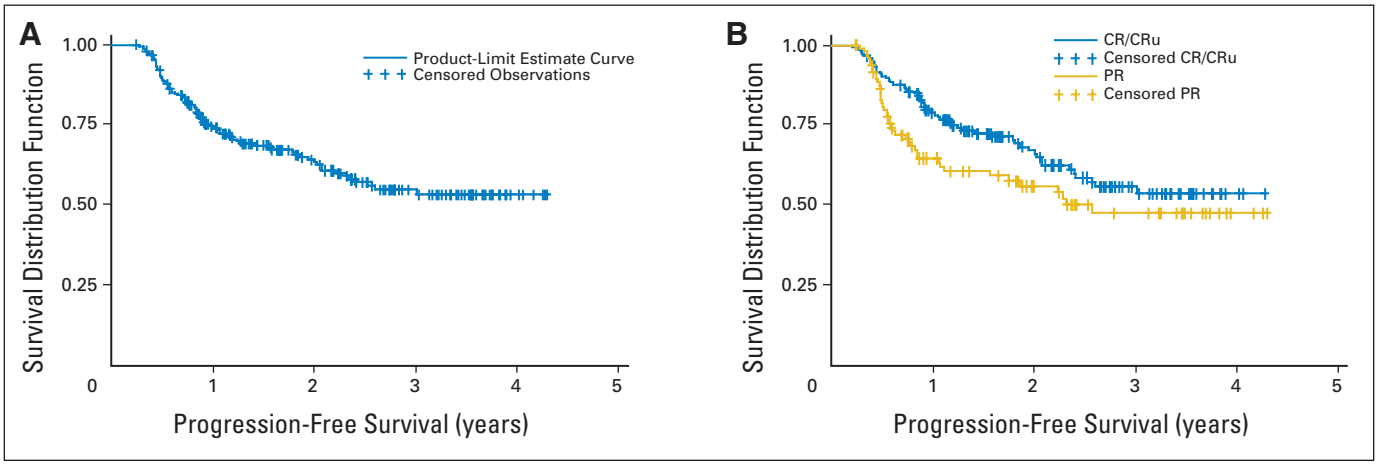

Fig 4. (A) Progression-free survival (PFS) of patients undergoing autologous stem-cell transplantation (intent to treat; n = 206). (B) PFS according to response after salvage regimen (including death) for all patients: complete response (CR) plus unconfirmed complete response (CRu; n = 147) and partial response (PR; n = 98).

R-ICE arm, and more patients required at least one platelet transfusion during the induction phase (57% in R-DHAP arm *v* 35% in R-ICE arm). In all, 90 serious adverse events occurred in 58 patients in the R-ICE arm, and 120 serious events occurred in 68 patients in the R-DHAP arm.

In both arms, the most common serious adverse events were infections, with a similar rate of infection as a result of neutropenia (16%) in both arms. Grade 3 to 4 nonhematologic toxicities were more severe in the R-DHAP arm and included grade 4 renal toxicity in 11 patients (Appendix Tables A4 and A5, online only). Patients who underwent BEAM followed by ASCT experienced the usual patterns of hematologic and nonhematologic toxicity, and three toxic deaths occurred.

DISCUSSION

In DLBCL, two populations are candidates for salvage treatment followed by high-dose chemotherapy and ASCT—patients who experience a relapse after achieving CR and those who do not achieve CR but are still responding to treatment. From the PARMA data,[6] patients experiencing early relapses less than 12 months after diagnosis have the same poor prognosis as incomplete responders. Such patients constituted 57% of all patients in the present study. Because this study was performed between 2003 and 2007, not all of the patients had access to rituximab as first-line treatment. This fact enabled us to prospectively enroll patients who did and did not have prior rituximab treatment (62% and 36%, respectively).

Because no randomized comparison of any salvage regimens had ever been previously reported, it was not clear which regimen was preferable for treatment of relapsed DLBCL.[12] The R-ICE regimen was chosen because we assumed that rituximab would improve its results, as suggested by the Memorial Sloan-Kettering Cancer Center.[13] Because DHAP has been widely used all over the world and was the salvage regimen of the PARMA study, it was used here as comparator.[5,12] Both regimens were supplemented with rituximab, which has been shown to improve treatment results of patients with relapsed DLBCL[11-13] not previously treated with rituximab.

The present results show a similar response rate of 63% for the two regimens, with a CR rate of only 38%, even after adjustment for mobilization failure. Furthermore, similar prospective mobilization failure rates of 10% were observed after both regimens. Only 50% of patients were able to undergo ASCT. Toxicities were similar, but there were more platelets and renal toxicity in the R-DHAP arm. An important finding was that several independent factors significantly affected response rates after salvage therapy, including saaIPI score, early relapse less than 12 months after diagnosis, and prior rituximab treatment. The same independent factors were found for OS, EFS, and PFS. R-ICE and R-DHAP gave similar results for all conceivable situations, thus demonstrating that it will be difficult to improve therapy without new drugs.

In this study, it was possible to identify a population with late relapse who benefited from the introduction of rituximab into their salvage regimen and exhibited an 80% response rate and a 3-year EFS ranging from 40% to 50%. Here, the standard treatment with ASCT reproduced the PARMA results.[6] However, there was a group of patients with a poor prognosis whose prior rituximab treatment was predictive, in cases of early relapse, of a response rate of 50% and 3-year EFS of only 20%. For these patients, the results of standard therapy should be improved, and new approaches are needed.

At the time of this analysis, there were not enough events (85 of 140 events) to determine the impact of rituximab administered as post-transplantation maintenance therapy. For patients who underwent transplantation, 3-year PFS was 53% (Fig 4).

Our results seem less favorable than those reported in a nonrandomized study[13] with R-ICE and in a study using high-dose rituximab before and after transplantation.[18] In the randomized CORAL study, the three courses of R-ICE were separated by a 3-week interval instead of 2 weeks, which may have helped to lower the CR rate. However, the patients in the present study differed from those in both of the previously cited studies because they had not had previous rituximab treatment and their response was evaluated by functional imaging.[13] We believe, however, that our results are more representative of the general population with relapsed DLBCL than those reported by single institutions with limited numbers of patients and no random assignment. When we looked at the initial prognostic parameters before failure/relapse according to prior rituximab treatment, patients who had received rituximab had more adverse factors, a finding likely to prove representative of the patients we will have to treat in the future.[19]

Consequently, new drugs designed to increase the response rate of salvage regimens and new approaches,[20] including allogeneic transplantation, should be explored.[21,22] In the era of antibody chemotherapy, novel targeted therapy resulting from better understanding of the biology of DLBCL, including studies of patient tumor specimens, will play a key role in these respects.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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